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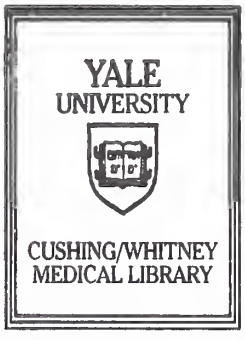
Trends in CA 125 Changes Within the Range of Normal as a Predictor of Ovarian Cancer Recurrence

Javier Lopez

YALE UNIVERSITY

2005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Trends in CA-125 Changes Within the Range of Normal as a Predictor of Ovarian Cancer Recurrence

A Thesis Submitted to the
Yale University School of Medicine
In Partial Fulfillment of the Requirements for the
Degree of Doctor in Medicine

By

Javier Lopez
2005

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TRENDS IN CA-125 CHANGES WITHIN THE RANGE OF NORMAL AS A PREDICTOR OF OVARIAN CANCER RECURRENCE.

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We conducted retrospective chart review aimed at gathering information about the trends of change in serum CA-125 levels within the range of normal in two patient populations (those who recurred after treatment and those who did not recur after treatment) and using this information to predict cancer recurrence.

Charts of patients diagnosed with epithelial ovarian cancer between 1998-2004 and who completed their treatment regimens were reviewed for CA-125 values and additional parameters. Only CA-125 values within the range of normal (<35 U/ml) during the follow-up period were analyzed.

The maximum absolute increase between any two consecutive CA-125 values was statistically significant ($p = 0.0004$) for the recurrence group. The maximum slope between two consecutive CA-125 values was significant ($p = 0.001$) in the recurrence group. Finally, the maximum sum of two consecutive slopes of CA-125 values was significant ($p = 0.003$) in the recurrence group.

Our data show that, for the patient treated for epithelial ovarian cancer and found to be free of disease after treatment, serial CA-125 value analysis within the range of normal will identify patients likely to continue on to develop epithelial ovarian cancer recurrence if the patient has two or more rising values, and/or if the absolute values rise 6.62 points or more.

Acknowledgements

Dr. Peter E. Schwartz, whose infinite knowledge this project could not have done without

Rohit Chandwani, for excellent statistical analysis

My family, for being my guiding light

Table of Contents

Introduction ——— Page 1

Statement of Purpose ——— Page 13

Methods ——— Page 14

Results ——— Page 16

Discussion ——— Page 23

References ——— Page 26

Introduction

It is estimated that 1%-2% of all women in Western countries will develop ovarian cancer, with the risk increasing after 40 years of age, and a peak incidence between 55 and 60 years of age. This estimation closely parallels the incidence of menopause in most Western countries. Furthermore, approximately 5%-10% of women in the United States will undergo a surgical procedure for a suspected ovarian neoplasm at some point during their lifetime, and 13%-21% of these women will be found to have an ovarian malignant neoplasm [1]. As of 2002 in the United States, 25,400 new cases of ovarian cancer appear yearly with a resultant 14,500 cases ending in death, making it the fourth most common neoplasm in women. However, ovarian cancer accounts for only 5% of all cancers in the US with the staggering figure that 1 in 58 women will develop the disease [1]. Across all age groups, women are not affected equally. The largest group of patients with ovarian cancer is the 60-64 year-olds. The incidence rate for patients 40-44 year-old is 15.7 per 100,000 and increases to 35 per 100,000 after the age of 50. Furthermore, elderly women are more likely than younger women to have advanced stages of disease at the time of diagnosis with a relative 5-year survival rate that is half that of women under the age of 65 [2].

A caveat of the above information is that the differential diagnosis of an adnexal mass varies considerably with the age of the patient. In fact, the index of suspicion for malignancy is much higher in both premenarchal and postmenopausal women in comparison to the reproductive-age population. Furthermore, many clinicians believe

that any palpable ovary in a postmenopausal patient suggests malignant change. After menopause, the size of the ovary diminishes to that of one not palpable during a routine pelvic examination. The possibility of malignant disease must therefore be carefully assessed when an ovary is palpable in a postmenopausal woman [1]. Non-gynecologic etiologies of an adnexal mass include fecal material in the sigmoid colon or cecum, inflammatory disorders of the bowel, the rare pelvic kidney, bladder disorders, and retroperitoneal disorders [3].

Among the most frequently found masses involving the adnexa are the non-neoplastic cysts related to the process of ovulation that are sometimes referred to as functional cysts (both follicular and corpus luteum types). They are by far the most common clinically detectable enlargements of the ovary occurring during the reproductive years [1]. Other common non-neoplastic findings are theca-lutein cysts, pregnancy, luteoma, sclerocystic ovaries, and endometriotic cysts. Theca-lutein cysts result from overstimulation of the ovary by human chorionic gonadotropin (hCG). Corpus luteum, follicular, and theca-lutein cysts are benign and represent an exaggerated physiologic response of the ovary [2].

Benign ovarian neoplasms can be either cystic or solid. Of the former, the most common are the serous and mucinous cystadenomas and cystic teratomas. Benign solid neoplasms of the ovary are usually of connective tissue origin. Malignant ovarian tumors are also either cystic or solid. Mucinous or serous cystadenocarcinomas comprise the majority of cystic malignancies, whereas solid ovarian malignancies tend to be adenocarcinomas from the ovary or metastatic to the ovary [4]. The diagnosis of an ovarian malignancy can only be made after both gross

and microscopic inspection. 20% of all ovarian neoplasms are pathologically malignant [1]. Furthermore, 85-90% of these are epithelial ovarian cancers. These are then subdivided into serous cystadenocarcinomas (42%), mucinous cystadenocarcinomas (12%), endometrioid adenocarcinomas (15%), undifferentiated adenocarcinomas (17%), and clear cell carcinomas (6%).

Screening for ovarian cancer continues to be a problem for physicians, for no time-tested tool exists. It has been suggested that every woman should have a periodic pelvic examination, pelvic ultrasound examination, and CA-125 test to make sure she does not harbor an occult ovarian cancer. However, it has been calculated that 10,000 routine pelvic examinations would be required to detect one early ovarian cancer in a population of asymptomatic patients [1]. In 1999, Jacobs and colleagues studied 22,000 women screened with CA-125 determinations. The patients studied were older than 45 years and post-menopausal. 47,775 tests were obtained with 1180 tests (2.5%) and 767 women (3.5%) having a concentration greater than or equal to 30 U/ml. The overall specificity and positive predictive value were 96.6% and 3.1%, respectively. Sensitivity at 1 year and 7 years of follow-up was 75% and 57%, respectively. Only 49 (6.3%) of women with elevated CA-125 (16%) had cancer, or 0.0022% of women screened [2]. The role of screening with CA-125 measurement in the general population of postmenopausal women appears limited.

Strategies for improving the effectiveness of ovarian cancer screening are plentiful. For instance, targeting populations at increased risk for the development of disease (e.g. individuals with a positive family history), or the use of multiple serum tumor markers. The latter strategy could potentially improve sensitivity and

specificity. However, Disaia reports that there is no evidence available yet that the current screening modalities of CA-125 measurement can be used effectively for widespread screening [1].

As is the case for most medical specialties, patients tend to seek care when symptoms develop. Some of the early symptoms associated with ovarian cancer include vague abdominal discomfort, digestive disturbances (e.g. dyspepsia), urinary frequency, and pelvic pressure. The above symptoms are produced as the tumor grows and compresses surrounding pelvic structures [4]. In fact, a high index of suspicion is warranted for all women between the ages of 40 and 69 who have persistent gastrointestinal symptoms that cannot be diagnosed [1].

Several diagnostic tools are available to assist the clinician in identifying ovarian cancer. Imaging tools include CT, MRI, and ultrasound. Intravenous pyelography and barium enemas may be used to analyze the surrounding pelvic structures. However, knowing the size, shape, contour, and general location of the mass within the pelvis can provide a great deal of information. Benign tumors are commonly smooth walled, cystic, mobile, unilateral, and smaller than 8 cm, whereas malignant tumors are usually solid or semisolid, bilateral, irregular, fixed, and associated with nodules in the cul-de-sac [1]. Size is an important determinant of malignant potential, for cysts <5 cm in diameter are rarely malignant. Size, however, does not indicate the severity of the disease. Koonings showed that the risk of malignant disease was 2.6-fold greater for women with bilateral neoplasms than for women with unilateral neoplasms [3]. Ascites is another finding highly indicative of malignancy. In addition, specific diagnostic assays are available for ovarian cancer. Tumor markers

commonly tested for are hCG, LDH, and AFP. CA-125, the focus of this paper, is associated with ovarian malignancies of the epithelial subset. Laparoscopy is useful in any situation in which the source of the pelvic mass is uncertain. Finally, the pelvic examination remains the most practical means of detecting early disease, even though it detects only 1 ovarian cancer in 10,000 asymptomatic women [5].

The staging of an ovarian malignancy is done surgically and can only be arrived at by histological analysis of samples taken during the procedure. The International Federation of Gynecology and Obstetrics produced the following nomenclature for the staging of ovarian cancer:

- Stage I disease = limited to one ovary
- Stage IA disease = limited to one ovary, no ascites, no surface involvement, capsule intact
- Stage IB disease = limited to both ovaries, no ascites, no surface involvement, capsule intact
- Stage IC disease = either stage IA or IB with ascites containing malignant cells or positive peritoneal cytology, capsule ruptured, or surface involvement
- Stage II disease = involving one or both ovaries with pelvic extension
- Stage IIA disease = extension or metastasis to fallopian tube or uterus
- Stage IIB disease = disease spread to other pelvic organs
- Stage IIC disease = either stage IIA or IIB with ascites containing malignant cells or positive peritoneal cytology, capsule ruptured, or surface involvement
- Stage III disease = tumor involving one or both ovaries with peritoneal implants outside the pelvis and or positive retroperitoneal and/or inguinal nodes
- Stage IIIA disease = tumor grossly limited to the true pelvis with negative nodes
- Stage IIIB disease = tumor of one or both ovaries with histologically confirmed abdominal implants none exceeding 2cm; nodes negative
- Stage IIIC disease = abdominal implants greater than or equal to 2cm; nodes positive
- Stage IV disease = distant metastasis

Treatment of ovarian cancer will be discussed according to the FIGO staging criteria outlined above. First line chemotherapy is aimed at curing disease, whereas therapy for relapse is mainly for palliation of symptoms. Stage I lesions tend to be treated with a total abdominal hysterectomy and bilateral salpingo-oophrectomy with careful surgical staging and a possible omentectomy. A platinum-based analogue alone or in combination with an alkylating agent or paclitaxel (Taxol) is used as post-operative chemotherapy for stage IB and IC disease [6]. Patients with stage IC disease are treated with multi-agent chemotherapy due to their 50% chance of recurrence [1]. Stage IIA and IIB disease is treated in much the same fashion as stage I disease, but a second-look operation may be considered to determine if the patient is clinically free of disease at the end of treatment. Stage III disease is treated the same, but more emphasis is placed on making every effort to remove the bulk of the tumor, and these patients receive multiple-agent platinum-based chemotherapy. Retrospective studies have shown these patients to have better prognoses with adjunctive therapy when they have minimal residual tumor remaining. Stage IV disease is difficult to manage due to the poor survival rate of this patient population, and surgery and chemotherapy also comprise the main arsenals.

During follow-up after treatment, the practice of analyzing tumor response to treatment rests on measurements of CA-125. CA-125 is an antigenic determinant defined by Bast by a murine immunoglobulin Igl monoclonal antibody that was raised against an epithelial ovarian carcinoma cell line [7]. Traces of the antigen are expressed in adult tissues derived from the coelomic epithelium, including mesothelial cells lining the pleura, pericardium, and peritoneum, as well as from the

epithelial component of the fallopian tube, endometrium, and endocervix [1]. CA-125 is not found in fetal or adult ovaries. Determinants are, however, expressed in >80% of nonmucinous epithelial ovarian cancers. [4]. Radioimmune assay has been developed by Bast to detect CA-125 in serum and body fluids. The day-to-day coefficient of variability for the assay is approximately 15%. Consequently, a doubling or halving of antigen levels has been considered significant. A cutoff of 35 U/ml is chosen for the upper limit of normal. 82% of patients who have surgically demonstrable epithelial ovarian cancer will have elevated CA-125 levels [1]. CA-125 levels can be altered in non-malignant conditions. For example, the mean CA-125 values of patients with liver cirrhosis or primary liver cancer can be very similar to that of patients with ovarian cancer [5]. Thus, serum CA-125 values are not useful for the diagnosis and/or screening of ovarian cancer. However, it is useful for following disease progression. Buller and colleagues have shown that a favorable outcome is associated with a steep regression curve of serum CA-125 levels after cytoreductive surgery and commencement of chemotherapy. These investigators demonstrated that patients in whom the CA-125 level reverts sharply to within the normal range by the third course of chemotherapy after surgery have a survival that is markedly and significantly improved over that of the patients who have an elevation of CA-125 levels before their fourth course of chemotherapy [6].

It has only been within the last two decades that a consensus has been reached about how to monitor ovarian cancer treatment in patients by using CA-125 levels. In 1997, Lukacsko and colleagues studied the predictive value of CA-125 during the post-operative chemotherapy and follow-up periods. They found the following: (1) a

decrease of CA-125 can predict the length of tumor-free survival, (2) the permanent high level of CA-125 is a signal of a recurrence within a few months after stopping therapy, and (3) in the case of an increase of the CA-125 level, an early recurrence can be expected [7]. This study was further verified by Meier in Germany in 1997 who recommended diagnosing recurrence and initiating therapy in cases of significantly raised CA-125 levels or elevated grade of CA-125 increase [8].

However, it was not until the work of Rustin and colleagues that a more working definition of response based on CA-125 levels was elucidated and extrapolated from the original World Health Organization guidelines of 1979 [9]. Rustin defined progression of disease as a rise from within the normal range to more than twice the upper limit of normal that was confirmed by a second sample at least as raised as the first elevated sample. This definition led to a false-positive rate of < 2%. Response according to CA-125 has occurred if either of the following criteria are met: (1) either a 50% response has occurred if there is a 50% decrease in serum CA-125 levels, or a 75% response has occurred if there has been a serial decrease in serum CA-125 levels of more than 75% over three samples [9]. The final sample has to be analyzed at least 28 days after the previous sample. In another study, Rustin showed that a rise in serial CA-125 levels during follow-up can predict recurrence of disease with a lead-time of several months [10]. Therefore, the median lead time between rise of CA-125 levels and clinical evidence of relapse was reported to be 63 days if the doubling from the upper limit of normal defines progression/recurrence and 4.5 months if just an elevation above 35 U/ml defines progression/recurrence [9].

In 1994, the European Organization for Research and Treatment of Cancer (EORTC), the National Cancer Institute of the US, and the National Cancer Institute of Canada Clinical Trials Group set up a task force with the main objective of reviewing the existing sets of criteria used to evaluate the response to treatment in solid tumors [11]. The result was the Response Evaluation Criteria in Solid Tumors (RECIST criteria), whose aim was to simplify the response evaluation of solid tumors through the use of unidimensional measurements and the sum of the longest diameters instead of the previous method of using two measurements and the sum of the products [11]. The following 2 conditions must be met for the RECIST criteria: (1) to assess the objective response of the solid tumor, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared, and (2) all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline [11]. The RECIST criteria for evaluation of target lesions and non-target lesions is discussed in Tables 1 and 2.

Table 1: RECIST Criteria for Target Lesion Evaluation

Response Type	*Definition*
Complete Response	Disappearance of all target lesions
Partial Response	At least a 30% decrease in the sum of the longest diameter of target lesions
Progressive Disease	At least a 20% increase in the sum of the longest diameter of target lesions

Stable Disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease

Table 2: RECIST Criteria for Non-Target Lesion Evaluation

Response Type	*Definition*
Complete Response	Disappearance of all non-target lesions and normalization of tumor marker levels
Incomplete Response/Stable Disease	Persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker level above the normal limits
Progressive Disease	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

The RECIST criteria were found to be 2.6 times less accurate than the CA-125 criteria at predicting survival [12]. However, on univariate analysis, both RECIST and CA-125 response were each significantly correlated with survival [12].

The above information provides insight into the controversy over specific definitions of stable, progressive, and recurrent ovarian cancer. Specifically for cancer recurrence, a doubling of CA-125 levels above the upper limit of normal is used. However, limited information is available on the early prediction of ovarian cancer recurrence through the use of tumor markers and other available modalities. The use of other biomarkers in conjunction with CA-125 has been suggested for early

recurrence prediction. For example, Shung Yeh and colleagues performed a retrospective study of 32 patients following both CA-125 and Tissue Polypeptide Specific Antigen (TPS). When compared with the follow-up modalities previously mentioned, TPS and CA-125 appeared lead-time effective with early diagnosis of recurrent ovarian cancer in 18 and 16 patients, respectively—a difference that was not statistically significant. However, the combination of the two biomarkers resulted in lead-time effects in 24 patients, suggesting the combination may be used as a possible tool in early prediction of recurrence [13]. The use of osteopontin has also been suggested for the same purpose. Osteopontin was found to be overexpressed in tumors and serum of women with a new diagnosis of ovarian cancer [14]. A 2004 study from Massachusetts General Hospital showed that serum osteopontin levels correlated with recurrent disease versus remission, presence of ascites versus absence, and bulky disease versus non-bulky disease [15]. CA-125 values yielded the same trends but with greater statistical significance. However, there is only one study to date that took a closer look at CA-125 levels alone in an attempt to identify a predictor of recurrence. Wilder and colleagues in 2003 attempted to determine the clinical implications of a progressively rising serum CA-125 level in the normal range in ovarian cancer patients with complete response to therapy. Eleven patients were identified, 1 with stage IIA disease and ten with stage IIIC disease. All patients subsequently developed recurrence of disease. The study found that in all the patients, three progressively rising serum CA-125 levels within the range of normal at 1- to 3-month intervals were associated with a high likelihood of tumor recurrence [16]. It is the purpose of our study to analyze the CA-125 values of patients who

completed treatment for epithelial ovarian cancer in an attempt to identify any specific changes between serial values of CA-125 that may be of utility in predicting recurrence of disease. The clinical utility of such information would be for specifically identifying what pre-recurrence changes in serial CA-125 values should prompt the clinician to suspect inevitable clinical recurrence of disease and prompt further investigation.

Statement of Purpose

Due to the lack of information on prediction of ovarian cancer recurrence in the current literature, our study was undertaken as a retrospective chart review to gather information about the rates of change in CA-125 levels within the range of normal in two patient populations: those who recurred after treatment and those who did not recur after treatment. Our hypothesis was that a difference exists within the rates of change between serial CA-125 levels amongst those patients with recurrence and those without. The normal range for CA-125 is <35U/ml, and this was the only range of values addressed because any value above 35 U/ml would be abnormal and can be considered to be a recurrence. Furthermore, we aimed at shedding light at the specific change that occurs in CA-125 levels within the range of normal of the recurrent patient population in an effort to use the specific change to predict a recurrence. Our null hypothesis is that there is no difference within the rates of change of CA-125 between the two patient populations. If our null hypothesis were to be rejected with statistical significance, then the clinician caring for the ovarian cancer patient can become knowledgeable of the meaning of specific changes in CA-125 and whether or not recurrence is likely in that patient.

Methods

The first step in the study was to receive approval from the Human Investigations Committee from Yale University School of Medicine. Form 12 was submitted to the committee and approval was given under HIC# 27174.

A list of patients was then received from the Gynecology Oncology Clinic in the Yale Physicians building. The names received were of patients diagnosed with epithelial ovarian cancer between 1998 and 2004 and who had completed their treatment. Treatment consisted of surgery, neo-adjuvant chemotherapy, adjuvant chemotherapy, or chemotherapy alone. A total of 169 patient names were acquired. The charts were then retrieved from the archives of Dr.'s Peter Schwartz, Thomas Rutherford, Setsuko Chambers, and Masoud Azodi. The charts of patients no longer under the care of the aforementioned physicians were retrieved from Jefferson Archives. The following data was collected for each patient:

- Age
- Weight
- Height
- BMI
- Date of Diagnosis
- Stage, Grade, and Histology of Tumor
- Treatment Type
- Date of Surgery
- Neo-adjuvant or Conventional Chemotherapy

- Type of First Chemotherapeutic Agent
- Date Began First Trial of Chemotherapy
- Status at Treatment Completion
- Time to Recur
- Method of Recurrence Diagnosis
- Type of Chemotherapeutic Agent After Diagnosed with Recurrence
- All CA-125 Levels (recorded in the chart before, during, and after treatment and before, during, and after each recurrence)

Preliminary data analysis for the above parameters included mean, median, maximum, minimum, and standard deviation. Additionally, a t-test was performed on all parameters that separated the groups into recurrence and non-recurrence. A thorough discussion of the specific data analysis can be found in the results section.

Results

The following is the demographic data collected prior to statistical analysis (Table 3). Data collected for 169 patients showed the mean age for the cohort to be 60 years with a standard deviation of 11.93 years, maximum of 92 years, minimum of 29 years, and median of 57.5 years. The mean weight for the group was 160.82 pounds with a standard deviation of 39.83 pounds, maximum 291 pounds, minimum 84 pounds, and median 152 pounds. Mean height was 63.94 inches with a standard deviation of 3.12 inches, maximum 70.5 inches, minimum 51.5 inches, and median of 163.83 inches. Finally, the mean BMI was 27.69 with a standard deviation of 6.60, maximum of 53.71, minimum of 15.89, and median of 26.59.

Table 3: Demographic data on original 169 patients

	Age	*Wt (lb)*	*Wt (kg)*	*Ht (in)*	*Ht (cm)*	*Area (m^2)*	*BMI*
Mean	60.10	160.82	73.01	63.94	162.40	2.64	27.69
SD	11.93	39.83	18.08	3.12	7.93	0.25	6.60
Max	92.00	291.00	132.11	70.50	179.07	3.21	53.71
Min	29.00	84.00	38.14	51.50	130.81	1.71	15.89
Median	57.50	152.00	69.01	64.50	163.83	2.68	26.59

Of the 169 patients, 72 had papillary serous histology, 23 had endometrioid histology, 8 had mucinous histology, 4 had adenocarcinoma histology, 7 had mixed mullerian histology, 33 had clear cell histology, 13 had Stage X disease with no histology

provided, 3 had mixed serous histology, 4 had transitional histology, 2 had sero-transitional histology, and 1 patient had serous with clear cell features (Table 4).

Table 4: Histologic data for original 169 patients

Histology	*No. of Patients*
Papillary serous	72
Endometrioid	23
Mucinous	8
Adenocarcinoma	4
MMT	7
Clear cell	33
Stage X	13
Mixed serous	3
Transitional	4
Sero-transitional	2
Serous with clear	1

162 patients received both surgery and chemotherapy. One patient received only surgery, 5 patients received only chemotherapy, and one patient opted for no treatment of any kind.

143 patients received adjuvant chemotherapy, while 24 received neoadjuvant chemotherapy and 2 did not receive any chemotherapy.

For the 169 patients, the mean number of CA-125 values per patient is 13.33 values with a standard deviation of 10.74 values, maximum of 63 values, minimum of zero values, and a median of 11 values.

68 of the 169 (40.23%) patients had a clinical recurrence, leaving 101 without recurrence. The data was analyzed for mean, median, variance, maximum value, minimum value, maximum absolute increase in U/ml, maximum absolute decrease in U/ml, maximum percentage increase, and maximum percentage decrease for all CA-125 values. The date of each recurrence was identified for each patient. The last CA-125 value before each recurrence was identified, and all values below the upper limit of normal for CA-125 (i.e. 35 U/ml) were eliminated. For the patients who did not have a recurrence, the longest stretch of CA-125 values was identified and isolated. For the patients with a recurrence, the stretch of values of CA-125 below 35 U/ml was isolated and identified. Patients without a stretch of at least two values were therefore excluded, for this data would not be suitable for analyzing the slope of the line of CA-125 values. This left 130 patients from the original 169, 54 with recurrence and 76 without (Figure 1).

Intervals between the initial date of diagnosis and each date of CA-125 collection were calculated. All date intervals were calculated relative to the first measurement of CA-125, for some patients had CA-125 values taken before a formal clinical diagnosis of ovarian cancer was produced. The purpose of calculating the date intervals was to scale the x-values as necessary for calculating the slope of the best-fit line through the CA-125 values of a given patient.

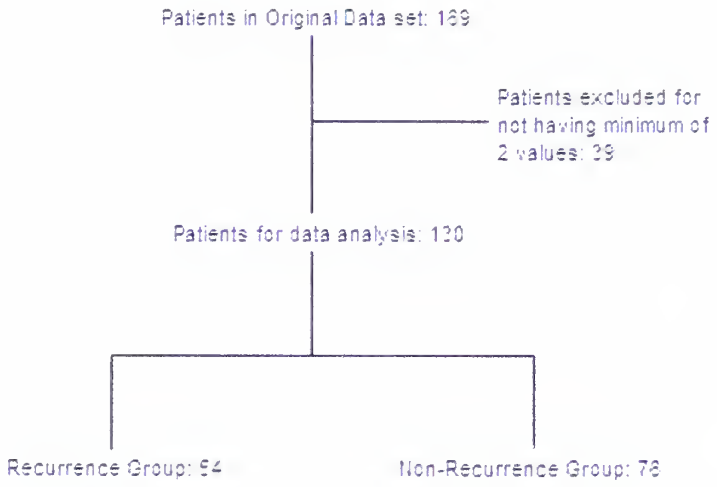
Patients in Original Data set: 169
Patients excluded for not having minimum of 2 values: 39
Patients for data analysis: 130
Recurrence Group: 54
Non-Recurrence Group: 76

Figure 1: Algorithm for Patients in Recurrence and Non-Recurrence Groups

The results of the analysis on the 130 patients can be found in Table 5 below. A t-test was performed on the data for determination of statistical significance for the following parameters: mean, median, variance, maximum value, minimum value, maximum absolute increase in U/ml, maximum absolute decrease in U/ml, maximum percentage increase, and maximum percentage decrease for CA-125 values. The p value for statistical significance was taken to be < 0.05.

The mean BMI for the group that recurred was 25.93 and 28.11 for the group without recurrence. These results were marginally statistically significant, with a $p = 0.049$. The mean CA-125 value in the recurrence group was 15.14 U/ml and 11.30 U/ml for the group without recurrence. This result was statistically significant with $p = 0.0005$. The mean variance for the recurrence group was 30.38 U/ml and 18.79 U/ml for the group without recurrence. This result was statistically significant with $p = 0.009$. The mean of the minimum CA-125 values in the recurrence group was 10.17 U/ml and 7.93 U/ml for the group without recurrence. This result was statistically significant with p =

0.035. The mean value of the maximum values for the patients in the recurrence group was 23.20 U/ml and 18.92 U/ml for the group without recurrence. This result was found to be statistically significant with $p = 0.003$. The mean value of the maximum absolute increase in CA-125 values for the recurrence group was 6.62 U/ml and 3.46 U/ml for the group without recurrence. This result was statistically significant with $p = 0.0004$. The mean value of the maximum absolute decrease of CA-125 values in the recurrence group was 6.59 U/ml and 7.42 U/ml for the non-recurrence group. This result was not found to be statistically significant, for the $p = 0.429$. The mean value of the maximum percentage increase for the recurrence group was 93.74% and 45.63% for the non-recurrence group. This result was found to be statistically significant with $p = 0.003$. The mean value for the maximum percentage decrease for the recurrence group was 33.39% and 37.99% for the non-recurrence group. This result was not statistically significant with $p = 0.342$. The mean value for the slope of the best-fit line of the recurrence group CA-125 values was –0.154 and –0.402 for the group without recurrence. This result was found not to be statistically significant with $p = 0.399$.

Table 5: Data for final group of 130 patients.

	Recurrence	*Non-recurrence*	*P value*
BMI (kg/m^2)	25.93	28.11	0.049*
Mean (U/ml)	15.14	11.30	0.0005*
Median (U/ml)	13.93	10.33	0.001*
Variance (U/ml)	30.38	18.79	0.009*
Minimum (U/ml)	10.17	7.93	0.035*

Maximum (U/ml)	23.20	18.92	0.003*
Max Abs Increase (U/ml)	6.62	3.46	0.0004*
Max Abs Decrease (U/ml)	6.59	7.42	0.429
Max Pct Increase (%)	93.74	45.63	0.003*
Max Pct Decrease (%)	33.39	37.99	0.342
Mean Slope++	-0.154	-0.402	0.399

* Denotes statistically significant $p<0.05$
++ Denotes slope of the best-fit line drawn through all CA-125 values for a given patient

The following set of statistics can be viewed in Table 6 below. A closer look was taken at the slope between any 2 consecutive values of CA-125 (y2-y1/x2-x1). The mean of these slopes for the recurrence group was –0.774, non-recurrence –1.349, and $p = 0.163$. The median values of these slopes for the recurrence group was 0.401, non-recurrence group 0.595, and $p = 0.456$. The minimum of these slopes for 2 consecutive CA-125 values in the recurrence group was –8.713, non-recurrence group –8.710, and $p = 0.999$. Conversely, the maximum for the same set was the recurrence group with 5.550, non-recurrence with 2.452, and $p = 0.001$ conclusive for statistical significance. The mean value of any two consecutive slopes of any two consecutive increasing CA-125 values was –0.603 for the recurrence group, -1.117 for the non-recurrence group, and $p = 0.170$. The median for these same slopes was –0.284 for the recurrence group, non-recurrence was –0.586, and $p = 0.343$. The minimum value of the sum of 2 consecutive slopes was –4.618 in the recurrence group, -5.011 in the non-recurrence group, and $p = 0.665$. The maximum value of the sum of 2

consecutive slopes was 2.524 for the recurrence group, 0.826 for the non-recurrence group, and p = 0.003 conclusive for statistical significance.

Table 6: Statistical analysis of the slope created from two consecutive CA-125 values

	Recurrence	*Non-recurrence*	*P value*
Mean Slope	-0.774	-1.349	0.163
Median Slope	0.401	0.595	0.456
Min Slope	-8.713	-8.710	0.999
Max Slope	5.550	2.452	0.001*
Mean of 2 Slopes	-0.603	-1.117	0.170
Median of 2 Slopes	-0.284	-0.586	0.343
Min of 2 Slope Sum	-4.618	-5.011	0.665
Max of 2 Slope Sum	2.524	0.826	0.003*

* Denotes statistically significant $p<0.05$

Discussion

Our analyses show ten total parameters to be statistically significant.

The mean BMI for patients in the recurrence group was 25.93 and 28.11 in the non-recurrence group, with $p = 0.049$. Though marginally statistically significant, taken in a clinical sense, this translates into heavier patients having a smaller likelihood of epithelial ovarian cancer recurrence. The mean value of CA-125 values within the range of normal (<35U/ml) was significantly higher in the recurrence group than in the non-recurrence group ($p = 0.0005$). This result, however, is expected given the nature of the direct correlation of rising and falling CA-125 values with disease progression and regression, respectively. The same is true of the median of CA-125 values within normal range ($p = 0.001$). The variance between CA-125 values was significantly greater in the recurrence group ($p = 0.009$). Thus, patients with greater changes between two consecutive values of CA-125 within the range of normal have a greater chance of recurring. Both the mean minimum and mean maximum CA-125 values were significantly higher in the recurrence group ($p = 0.035$ and $p = 0.003$, respectively); again, this result is as expected according to natural CA-125 trends in disease. The maximum absolute increase between two consecutive CA-125 values within the range of normal was shown to be statistically significant in the recurrence group ($p = 0.0004$). Therefore, a rise of 6.62 U/ml between two consecutive CA-125 values within the range of normal is predictive of future disease recurrence. On the other hand, a rise of 3.46 U/ml is predictive of non-recurrence. Furthermore, the maximum percentage increase between two consecutive CA-125 values was also statistically significant in the

recurrence group ($p = 0.003$). Thus, a rise of 93.74% from one CA-125 value to another within the range of normal is a predictor of future disease recurrence, whereas a rise of 45.63% predicts no recurrence of disease.

The problem arises, however, of the ability of CA-125 to be falsely elevated due to non-gynecologic malignancy-related conditions. Therefore, the slopes between all consecutive points of CA-125 values within the range of normal for a given patient were calculated. The maximum value of the slope between any two consecutive points was found to be significantly greater in the recurrence group ($p = 0.001$). In other words, a slope of 5.550 between two consecutive CA-125 values within the range of normal predicts future disease recurrence. In addition, in an effort to ameliorate the aforementioned problem, the sum of two consecutive slopes (four CA-125 value-analysis) for the range of CA-125 values within normal for a given patient was obtained. The maximum of the sum of two consecutive slopes was found to be statistically significant in the recurrence group ($p = 0.003$). Therefore, two consecutive rising values (mean maximum consecutive slope sum of 2.524) in our patient population was statistically significant for disease recurrence.

In summary, for the patient treated for epithelial ovarian cancer and found to be free of disease after treatment completion, serial CA-125 value analysis within the range of normal will show that if the patient has two or more rising values, and if the values rise 6.62 points or more, then the patient is likely to continue on to develop epithelial ovarian cancer recurrence. This information should fine-tune the physician's interpretation of CA-125 values obtained during the follow-up period after disease treatment. However, within our cohort of patients, there existed patients with increases in CA-125 values more

than 6.62 U/ml who did not recur. Similarly, there also existed patients with increases of less than 6.6.2 U/ml who did recur. Considering this information, it would be beneficial and necessary to perform a prospective study to further evaluate our findings. At the very least, our study verifies that there were two distinct patient populations in our study who were not to be considered equally for treatment, secondary to recurrence risk.

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